

## REMARKS

### Section 102 Rejection:

Claims 1, 7 and 10 stand rejected under 35 USC 102(b) over Yalkowsky (US 4,489,026). Applicants respectfully traverse the rejection as Yalkowsky does not disclose all the elements of the claimed invention.

Yalkowsky describes production of tablets produced by direct compression of a finely divided powder of a highly absorbent excipient insoluble in the solvent, and wherein the excipient is coated with active principle. See Specification, page 4, lines 15 – 24, citing Yalkowsky. However, the powder of Yalkowsky is distinct from the neutral microgranules of the claims. One of ordinary skill in the art would understand that Yalkowsky's powder is not interchangeable with the neutral microgranules of the instant invention.

As stated in the instant specification, neutral microgranules of the claims are as defined by the US Pharmacopoeia (USP XVII, 1990):

- spherical granules comprising between 62.5 and 91.5 % sucrose, the remainder being composed essentially of starch;
- of uniform size (with a low variation of range of size); and
- between 100 and 2000<sub>μ</sub>m. (Neutral microgranules between 200 and 2000 <sub>μ</sub>m are commercially available.)

See Specification, p. 7, lines 18 – 34.

In contrast, the particles of Yalkowsky's powder are much smaller. Their maximum mean diameter is between 0.5 <sub>μ</sub>m and 10 <sub>μ</sub>m. Further, one of skill in the art would understand that the particulates of Yalkowsky's powder are neither spherical nor of uniform size.

The variation in form and size has significant functional consequences. The claimed neutral microgranules provide greater uniformity of surface area and of active principle attached to each neutral microgranule, and thus greater uniformity of dosage. Yalkowsky does not teach the use of such uniform neutral microgranules; and thus, the formulations of Yalkowsky would not have the advantages of the claimed formulations.

The teaching of Yalkowsky does not include all of the limitations of claims 1, 7, and/or 10, and thus Yalkowski does not anticipate any of those claims. Applicants respectfully request reconsideration and withdrawal of the § 102(b) rejection.

Section 103 Rejection:

Claims 2-6, 8-9, and 11-16 stand rejected under 35 USC § 103 over Yalkowsky in view of Maish (US 4,983,399). Applicants respectfully traverse the rejection as one of ordinary skill in the art would not have been motivated to combine Yalkowsky with Maish; and, even if so motivated, there has been no showing that such combination would have produced the claimed invention.

Maish describes direct compression of a carrier particulate composition comprising: (1) a cellulose carboxylic acid ester powder and (2) a lubricant.

However, in Maish the active compound is not attached as a coating onto particulates of the carrier composition. Rather, the active compound, as a powder, is blended with the carrier composition and the mixture is compressed into tablets.

See Examples 7, 8, & 9.

Further, the tablets of Maish contain high concentration of active compound, *i.e.*, 40 % by weight of tablet. Col. 5, lines 21 – 24. In contrast, the instant claims

recite low dose tablets (less than 40 mg/g, or less than 4 % by weight of the tablet). One of ordinary skill in the art would not have been motivated to look to a reference such as Maish directed to tablets having high concentration of active compound in formulating a tablet having very low concentration of active compound.

The rejection also asserts that one of skill in the art would have been motivated to increase the 5 - 10  $\mu$ m particle size of Yalkowsky by increasing spraying time to a range said to be supported by Maish. Specifically, the Official Action asserts "the Maish '399 patent teaches that a direct compression microparticulate tableting composition having a mean particle diameter in the range from about 50  $\mu$ m to about 300  $\mu$ m results in a free-flowing composition...." Official Action of 1/24/2006, p. 7. However, the passage from Maish refers to the size of the lubricant particles, not the cellulose ester powder particles (Col. 4, line 26). Accordingly, Maish does not provide motivation to modify the spraying time of Yalkowsky to achieve the claimed range of particle sizes, nor does it establish that such modification could even produce the claimed size ranges.

The Official Action acknowledges that Yalkowsky states that the 5 - 10  $\mu$ m particle size range is variable up to about 100%, and asserts that increased spraying time would produce particles of greater diameter. However, the Official Action fails to provide the motivating teaching for prolonging the spraying time or increasing the particle size; and fails to identify any teaching or suggestion supporting the assertion that merely increasing the spraying time can produce particles in the claimed range. Accordingly, the Official Action fails to make a proper prima facie case.

Further, one of ordinary skill in the art would not have been motivated to combine Yalkowsky with Maish because:

- in Maish, the active compound is not attached as a coating to the carrier powder, whereas in Yalkowsky it is;
- Maish relates to high dose tablets, whereas Yalkowsky relates to low dose tablets; and
- Maish does not provide the missing motivation to increase the particle size of Yalkowsky.

Even if one of ordinary skill in the art had combined the two references, there is no showing that the references would have been combined in the manner relied upon in the rejection; and there is no showing that had such a combination been made, one would have arrived at the invention as claimed. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Conclusion:

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of all outstanding rejections. Applicants submit that the claims are now in condition for allowance, and respectfully request formal notification to that effect. If, however, the Examiner perceives any impediments to such a notice of allowability, whether substantive or formal, the Examiner is encouraged to call Applicants' attorney at the number provided below. Such informal communication will expedite examination and disposition of this case.

Respectfully submitted,

BUCHANAN INGERSOLL PC

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By:

  
Brian R. O'Shaughnessy  
Registration No. 32,747

P.O. Box 1404  
Alexandria, VA 22313-1404  
703.836.6620